Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 4-12, 14, 20-41, 44-47, 50-54, 57 and 63-70 are pending in the application, with claims 1 and 63 being the independent claims. Claims 13, 15, 16, 18, 19, 42 and 43 are sought to be canceled and reiterated as new claims 64-70, respectively. New independent claim 63, encompassing the subject matter of claims 13, 15, 16, 18, 19, 42 and 43, is sought to be added. Claim 57 is sought to be amended. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Rejections Under 35 U.S.C. §112

Claim 57 was rejected under 35 U.S.C. § 112, first paragraph, because the specification "does not reasonably provide enablement for a method of preventing (not even occur at the first time) pain by administering the agent to the subject." Office Action, page 3, lines 7-8. Applicants respectfully traverse this rejection.

Claim 57 has been amended to delete the term "or preventing." Applicants respectfully submit that the rejection of claim 57 under 35 U.S.C. § 112, first paragraph, has been rendered moot and should be withdrawn.

II. Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 1, 4-12, 14, 20-41, 44-47, 50-54 and 57 under 35 U.S.C. § 103(a) as being unpatentable over Foster *et al.* (WO 96/33273) taken with Sharon *et al.* (*FASEB Journal 4*: 3198-3208 (1990)). Office Action, page 6, lines 16-18. Applicants respectfully traverse this rejection.

A. Legal Principles

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

M.P.E.P. § 2143 ("Basic Requirements of a *Prima Facie* Case of Obviousness") (August 2001). *See also In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success viewed in light of the prior art.")

B. The Primary Reference: Foster et al.

The Examiner is of the opinion that:

> Foster *et al.* teach an agent containing lectin (page 13, lines 9-13) as the targeting moiety (TM) and a modified clostridial neurotoxin such as LH_N (including L-chain and its functional fragment, claims 1, 24-31, 35, 39, 46, 50), the clostridial neurotoxin having H_C chemically modified to reduce its ability to bind the receptor (claims 20-23, 36), and a hybrid molecule of a modified heavy chain (H_C being modified) of a clostridial toxin with a light chain of a different clostridial toxin (page 13, line 18-page 14, line 19; claims 32-34) can be obtained by covalent[] attachment of a TM to a modified clostridial neurotoxin using linkage including one or more spacer regions (page 14, lines 1-9; claims 37, 40, 47) or can be expressed recombinantly as a fused protein (page 14, line 29-page 15, line 4; claim 38, 41, 50). This agent can bind to a binding site on the surface of sensory neurons (page 12, lines 25-28) and reduce or preferably prevent the transmission of pain signals from nociceptive afferents to projection neurons (page 7, lines 15-17; claims 44-45), therefore it can be used for controlling the transmission of sensory information or pain signals from a nociceptive afferent to a projection neuron (claims 51-54 and 57). However, Foster *et al.* do not disclose using a specific lectin such as galactose-binding lectin in preparing the agent.

Office Action, page 6, line 19, through page 7, line 8. Applicants respectfully disagree with the Examiner's characterization of Foster *et al.*

Foster *et al.* discloses "an agent which can inhibit the release of at least one neurotransmitter or neuromodulator or both from the synaptic terminals of nociceptive afferents" (*see* page 11, lines 1-3). As the Examiner acknowledges, "Foster *et al.* do not disclose using a specific lectin such as galactose-binding lectin in preparing the agent." Office Action, page 7, lines 7-8. This deficiency is not cured by the other reference cited by

the Examiner. Thus, claims 1, 4-12, 14, 20-41, 44-47, 50-54 and 57 are not obvious in view of Foster *et al.* and Sharon *et al.*

C. The Secondary Reference: Sharon et al.

The Examiner is of the opinion that "[a]t the time [the] invention was made, it would have been obvious to one of ordinary skill in the art to make the agent taught by Foster *et al.* and to use [a] specific lectin such as galactose-binding lectin taught by Sharon *et al.*" Office Action, page 7, lines 13-15. Applicants respectfully disagree.

The Examiner makes two assertions in support of this opinion. The first assertion is that "galactose-binding lectins are widely available in legume plants (see Table 1 of Sharon *et al.*)." Office Action, page 7, lines 15-16. This observation, regardless of whether it is true or not, is insufficient to establish a *prima facie* case of obviousness. The mere existence of a possible combination does not establish a *prima facie* case of obviousness. "[A] showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding.'" *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25 (Fed. Cir. 2000) (quoting *C.R. Bard, Inc., v. M3 Systems, Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.").

The Examiner's second assertion is that galactose-binding lectins "can serve as a cell-recognition molecule *for the agent*." Office Action, page 7, lines 16-17 (emphasis added).

In support of this assertion, the Examiner summarizes three portions of Sharon *et al.* as follows:

> Sharon *et al.* teach certain oligosaccharides such as complexed type oligosaccharides with terminal galactose residues can act as multivalent ligands that cross-link and precipitate galactose or N-acetylgalactosamine specific lectins such as soybean agglutinin, or those of different Erythrina species (page 3200, right column; Table 1; claims 4-12), and the S-type lectins in animals that have a specificity for β-galactosides (page 3198, right column; claim 14).

Office Action, page 7, lines 8-13. Applicants respectfully disagree with the Examiner's analysis and conclusions.

Sharon *et al.* is a scholarly review article entitled "Legume lectins – a large family of homologous proteins." Sharon *et al.* teaches that lectins, including legume lectins, "are currently attracting much interest, primarily because they serve as invaluable *tools in diverse areas of biological and medical research* (page 3198, col. 1, last three lines, and col. 2, first line) (emphasis added) (*see* page 3198, col. 2, lines 1-19 for elaboration).

Sharon *et al.*, page 3200, col. 2, lines 6-25, states that:

> Recent work has shown that certain oligosaccharides that contain multiple binding sites for lectins can precipitate the lectins from solution. For example, bi, tri-, and tetrabranched (antennary) complex-type oligosaccharides with terminal galactose residues act as multivalent ligands that cross-link and precipitate galactose (and *N*-acetyl-galactosamine)-specific lectins, such as soybean agglutinin or those of different *Erythrina* species. Similarly, oligomannose and bisected hybrid-type glycopeptides that are bivalent for concanavalin A (Con A) precipitate the lectin. Studies with mixtures of such oligosaccharides and lectins have revealed that the cross-linking reaction results in the formation of homopolymeric, and not heteropolymeric, complexes with the lectin. Thus, the specificity of interactions of lectins with multivalent oligosaccharides is far greater in the formation of cross-linked complexes than in that of non-cross-linked ones. These results have important implications for the biological

> functions of cell surface receptors for lectins, as well as for other molecules.

(citations omitted). Sharon *et al.* offers no explanation as to what the important implications of this research might be. Sharon *et al.* does not teach or suggest that lectins isolated from *Erythrina* species (or any other species) might be of any use other than as a tool for biological or medical research. This is at best an indefinite suggestion to experiment with lectins.

Sharon *et al.*, Table 1, at page 3199, discloses the origin and specificity of some purified lectins from legume seeds. Table 1 illustrates that previous researchers have grouped purified legume lecithin into five non-exclusive specificity groups: I, mannose (glucose); II, galactose/*N*-acetylgalactosamine; III, *N*-acetylglucosamine; IV, L-fructose; and X, interact only with oligosaccharides. In Table 1, Sharon *et al.* does not teach or suggest that the purified lectins might be of any use other than as a tool for biological or medical research.

Sharon *et al.*, page 3198, col. 2, lines 27-42, states that:

> Among animal lectins, two distinct families have been identified: 1) the C type (Ca^{2+} dependent), containing both membrane-bound and soluble lectins with diverse carbohydrate specificities; and 2) the S type (thiol dependent or soluble), consisting of lectins that share a specificity for β-galactosides. Lectins of the latter type are developmentally regulated and differentially expressed in different tissues.
>
> The existence of such homologous families demonstrates that these proteins have been conserved throughout evolution and argues strongly that they must have an important function (or functions) in nature. Although this function is not known with certainty, it is generally believed that lectins serve as cell-recognition molecules.

(citations omitted). Thus, Sharon *et al.* discloses that S type lectins have a specificity for β-galactosides, are differentially expressed in different tissues, and have a function that is not known with certainty. Sharon *et al.* might be cited for the proposition that "it is generally

believed that lectins serve as cell recognition *molecules"* (*see* page 3198, col. 2, lines 40-41) (emphasis added). However, Sharon *et al.* does not teach or suggest the use of lectins as a portion of a larger, non-natural, biologically active agent.

None of the sections of Sharon *et al.* that have been cited by the Examiner provide any motivation for one of ordinary skill in the art to combine the teaching of Sharon *et al.* with that of Foster *et al.* Therefore, the Examiner has not established a *prima facie* case of obviousness. *See Brown & Williamson Tobacco Corp.*; *In re Dembiczak.* It follows that claims 1, 4-12, 14, 20-41, 44-47, 50-54 and 57 are not obvious in view of Sharon *et al.* and the other reference cited by the Examiner.

D. Summary

Applicants respectfully submit that the rejection of claims 1, 4-12, 14, 20-41, 44-47, 50-54 and 57 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

III. Additional Rejections

A. Rejected Claims 13, 15, 16, 18, 19, 42 and 43

The Examiner has rejected claims 13, 15, 16, 18, 19, 42 and 43 "because they are dependent upon a rejected claim." Office Action, page 7, lines 19-20. Applicants respectfully traverse this rejection.

Claims 13, 15, 16, 18, 19, 42 and 43 have been canceled. Applicants respectfully submit that this rejection has been accommodated and should be withdrawn.

B. New Claims 63-70

New independent claim 63, encompassing the subject matter of claims 13, 15, 16, 18, 19, 42 and 43, has been added. Claims 64-70 are directly or indirectly dependent upon new claim 63. Applicants respectfully submit that new claims 63-70 are fully in condition for allowance.

IV. Other Matters

Applicants note that page 1 of the Form PTO-1449 submitted with the Third Supplemental Information Disclosure Statement filed on September 10, 2002 (citing Document AT7, Black, J.D., and Dolly, J.O., "Interaction of ^{125}Labeled Botulinum Neurotoxins with Nerve Terminals. I. Ultrastructural Autoradiographic Localization and Quantitation of Distinct Membrane Acceptors for Types A and B on Motor Nerves," *J. Cell Biol. 103*:521-534, The Rockefeller University Press (1986)), was not returned to Applicants. Applicants respectfully request that a copy of this page of the Examiner-initialed Form PTO-1449 be returned to Applicants.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

Claims 13, 15, 16, 18, 19, 42 and 43 have been canceled.

Claim 57 has been amended as follows:

57. (Thrice amended) A method of alleviating [or preventing] pain which comprises administering to a subject in need thereof an effective dose of the agent according to Claim 1 by a route selected from the group consisting of intrathecal, subcutaneous, and epidural routes, thus alleviating [or preventing] pain.

Claims 63-70 have been added.